Role of Renal Nerves in a Preclinical Model of Advanced Autosomal Recessive Polycystic Kidney Disease

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Autosomal recessive polycystic kidney disease (ARPKD) is a genetic disease where renal cyst growth results in cardiorenal dysfunction. We revealed a role for renal nerves in the early phase renal cystogenesis in the PCK rat model of ARPKD. Total renal denervation (T-RDNx) and afferent denervation (A-RDNx) mitigated cystogenesis from 4 weeks of age (W4) through W10, demonstrating renal afferent nerves' contribution to cystogenesis. Here, we evaluated the role of renal nerves in cystogenesis and cardiorenal dysfunction in a later disease stage, in 24-week-old PCK rats. We hypothesized T-RDNx, but not A-RDNx, would improve renal function and decrease systolic blood pressure (SBP), but neither would decrease cystogenesis.

To test this hypothesis, PCK rats (Age: Week 24; W4) were treated with T-RDNx (n=12;7M/5F), A-RDNx (n=15;7M/8F), or sham (n=13;6M/7F) surgery. Cardiorenal function was monitored through W30. SBP was collected via tail cuff. Renal function was assessed by serum creatinine and blood urea nitrogen. W30 kidney tissues were assessed for cystic index (%cystic area). Effects were analyzed by two-way ANOVA with Bonferroni post hoc ($p<.05$). Data presented as mean±SEM.

Pre-treatment, cardiorenal function was not detectably different between groups. Following treatment, SBP decreased in T-RDNx rats at weeks 1 (-20.1±3.4 mmHg), 2 (-15.4±3.5 mmHg), and 3 (-13.6±2.6 mmHg) versus Sham (-2.27±5.3 mmHg; -0.9±4.1 mmHg, 0.1±2.7 mmHg), but renal function was not different between groups. Cystic index decreased in T-RDNx (17.2±1.7%) and A-RDNx (17.4±1.9%) compared to Sham (24.0±2.4%).

First, these data support our hypothesis that SBP would decrease only with T-RDNx. Yet, in contrast to our hypothesis, cystogenesis decreased in both T-RDNx and A-RDNx groups in advanced ARPKD. These studies complement our previous findings and support the overarching hypothesis that afferent renal nerves contribute to renal cystogenesis in early- and late-phase ARPKD progression. Further studies into afferent nerve-mediated cytogenic signaling are underway.

Funding Sources: PCK RRC Pilot and Feasibility Award (U24DK126110); PKD Foundation (1022534)